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| 14. ABSTRACT After initiating the DOD funded project TGC established relationships with Davos, Niels-Clauson-Kaas (NCK), and Metrics, for cGMP drug substance synthesis, and formulation (tablet; drug product) development, respectively. GMP API was manufactured, an HPLC assay was established and validated, and formulation development work was initiated. | | | | | |
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Introduction

Start Date: August 2008

Objective Provide product for a Phase I study in ALS subjects testing safety and efficacy of Apocynin.

Product Profile:

| Description | Oral dosage formulation for Apocynin (API) |
|-----------------------------|--|
| Composition Presentation | Solid (tablet) Storage: Ambient Final Formulation: To be determined |
| Administration | Oral dosage |
| Goal | To develop a therapeutic for Amyotrophic lateral sclerosis (ALS), and enhance life expectancy and quality of life. |

Body

After initiating the DOD funded project TGC established relationships with Davos, Niels-Clauson-Kaas (NCK), and Metrics, for cGMP drug substance synthesis, and formulation (tablet; drug product) development, respectively.

Key Research Accomplishments

cGMP –API Manufacture

NCK was successful in establishing an organic synthesis of the drug substance, first as a technical development exercise and to support product identity and stability assay development. 126 grams of technical-grade material was produced. An additional 109 grams of material was synthesized for use as assay reference material. Approximately 8 kilograms of drug was then synthesized using the cGMP synthesis methods for use in formulation development. An additional 10.3 kilograms of cGMP drug substance was synthesized, tested, released and placed on stability. An HPLC assay was developed and validated to support identity, stability and purity.

These activities were paid by TGC. TGC and Univ of Iowa have reached an agreement whereby Univ. of Iowa will reimburse TGC using funds from the contract. TGC will transfer this drug substance to Univ of Iowa. NCK continues to perform stability studies on the API and no adverse trends were noted.

Formulation Development for Drug Product

Metrics had initiated formulation for the drug substance. This consists of a wide-ranging excipient compatibility study (one and 2 month time-point data available support further development) followed by tablet development. Tablets may accommodate, in some cases, 1100-1200 mg (much of which could be API), whereas a capsule just cannot handle such a load. While it is true that for early phase development, a simple blend and fill capsule approach is preferred, the high drug load combined with the high daily dosing regimen pushed us into thinking about a tablet as the preferred dosage form. Tablet development work testing various recipes, using wet or dry granulation was conducted on tablets containing 400 mg of API and weighing 600 mg have demonstrated unacceptable friability and capping in all cases. Based on these data it was decided that the best approach would be API in a capsule for the initial Phase 1 study. The tablet dosage form was selected due to the potentially high drug load required for the clinical study. The high drug load required is based on John Englehardt's pharmacology studies (efficacious dose 150-300mg/Kg in mice). Apocynin is not very soluble with an IC₅₀ of 10µM measured in in vitro studies with activated PMN.

Formulation Development for Preclinical Toxicology studies

To initiate preclinical studies in support of IND filing oral gavage formulation development was initiated at Charles River Laboratories. The formulation developed was tested *in vivo* in a preliminary PK study. The pharmacokinetic behavior of apocynin following intravenous administration (using control formulation) appears to be that of a very rapid distribution phase where Apocynin moves out of the circulation into the tissues, followed by a much slower elimination phase. The pharmacokinetic data following oral dosing is less clear as it is not possible to reasonably assess whether C_{max} occurs at 15 min or earlier as there is also a rapid distribution phase in effect at or before the first time point following oral dosing. A rough estimate of 9-11% bioavailability was calculated; however, it is this is an estimate of bioavailability, due to the lack of early time points for the PO route. Comparison of the concentration of Apocynin in the brain at three time points relative to plasma suggests that the brain concentration is lower than that of the plasma but is difficult to assess due to the limited number of time points and the variability as the concentrations approach the limit of detection.

Reportable Outcomes:

None

Conclusion

Excellent progress was made in the manufacture, testing, release and stability of the API to be used in a clinical trial. Work progressed on formulation development, and this work will continue in the future after the award is transferred to the University of Iowa.

As of March 2009, due to financial constraints at TGC no additional work was performed on this project. This project is now being transferred to Univ of Iowa, with Barrie Carter as the P.I.

References

None

Appendices

None

Supporting Data

None